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Research Article

# Synthesis and antihyperlipidemic activity of Dibenz[c,e]azepine-5,7-dione derivatives in Triton WR-1339-induced hyperlipidemic rats

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### ABSTRACT

The structural requirements for decreasing cholesterol and triglyceride levels remain largely uninvestigated. Thus a systematic investigation of certain N-substituted dibenz[c,e]azepines is necessary. Nine compounds of N-substituted derivatives of Dibenz[c,e]azepine-5,7-Dione were synthesized and they were tested for antihyperlipidemic activity. Compounds synthesized (C-1, C-3, C-4 and C-5) significantly lowered the serum total cholesterol, triglyceride and LDL (low density lipoprotein) levels and also improved the HDL (high density lipoprotein) level in Triton-WR 1339 induced hyperlipidemic rats.

**Keywords:** antihyperlipidemic activity, lipids in plasma, high density lipoprotein

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### INTRODUCTION

Cardio vascular diseases are leading cause of death in both industrialized and developing nations. It also significantly contributes to the mortality and morbidity of human in the industrialized nations<sup>1,2</sup>. Hyperlipidemia is one of the important risk factors involved in the development of cardiovascular disease. Hyperlipidemia is defined as an elevation of lipids in plasma<sup>3</sup>. Several studies have showed that an intimate correlation exists between coronary heart diseases and hyperlipidemia, consequently a rational approach to the treatment and prevention of coronary heart diseases could be by decreasing any elevated levels of lipids in plasma<sup>4,5</sup>. Although there are many studies have been conducted to evaluate the potential hypolipidemic effects of synthetic and naturally occurring compounds, it is still imperative to find more effective and nontoxic drugs.

In searching for a new class of antihyperlipidemic agents, dibenz[c,e]azepines-5,7-dione derivatives have been found to possess antihyperlipidemic action via lowering the triglycerides and cholesterol levels. The detailed study of cyclic imides showed that seven-member cyclic imides such as dibenz[c,e]azepines-5,7-diones could possess the antihyperlipidemic activity<sup>6</sup>. In the present study, we aimed to synthesize a new series of dibenz(c,e)azepines-5,7-diones derivatives and to investigate their hypolipidemic activity using Triton WR-1339 induced hyperlipidemic rats as a model.

### MATERIAL AND METHODS

#### Chemicals and instruments

All chemicals and solvents used were of analytical grade and purchased. The melting points were determined in open capillaries and are uncorrected. Purity of the compounds was checked by thin layer chromatography (TLC). TLC was performed on precoated (0.25 mm)

silica gel GF plates (E. Merck, Germany). The infra red spectra were recorded by using ATR-IR model ALPHA Bruker, Germany. <sup>1</sup>H NMR spectra were recorded on a BrukerAvance II 400 MHz NMR spectrometer; Chemical shifts are expressed in ppm with reference to TMS.

### Animals

Healthy Wistar male rats weighing 210-230 g were used. The animals had free access to a standard commercial diet and water *ad libitum* and were kept in rooms maintained at 25 °C with a 12-h light/dark cycle. The animals were used after an acclimatization period of 7 days to the laboratory environment. The experiments were performed during the light portion (0800–1600 h). The experimental protocol and procedures used in this study were approved by IAEC of Lachoo Memorial College of Science and Technology, Pharmacy Wing, Jodhpur.

### Synthesis and scheme

The scheme of synthesis of test compounds is presented in Figure 1-2. Diphenic anhydride was prepared from reported procedure. A mixture of diphenic anhydride (11.21 gm, 0.05 mole) and appropriate aromatic and hetero-aromatic amine (0.05 mole) in Xylene (150 ml) was heated under reflux for 4-5 hours with stirring. The mixture was cooled and the resulting solid product (a diphenic acid derivative) was filtered, dried and transferred to 250 ml RBF containing acetic anhydride (150 ml) and anhydrous sodium acetate (10 gm) equipped with reflux condenser. The mixture was heated for 3-4 hours and transferred to 500 ml ice cooled water. The precipitate was washed with water and crystallized with ethanol<sup>7,8</sup>

The compounds were characterized by qualitative elemental analysis, melting point and spectroscopic analysis<sup>9</sup>. Melting point ranges of newly synthesized compounds were determined by open glass tube using visual melting apparatus and are uncorrected. The temperature at which compound started melting to the temperature at which it completely melted was taken as the melting point range. All the new derivatives were subjected to elemental detection for elements like Chlorine, Nitrogen and Sulphur. Qualitative assessment for the presence of these atoms was done by preparing Lassaigne extract of the compounds. IR spectrum of

compounds was recorded on an ATR Spectrophotometer. <sup>1</sup>H-NMR spectrum of newly synthesized compounds was recorded on NMR spectrometer at 400MHz in chloroform and Dimethyl sulfoxide (DMSO) using Tetramethylsilane (TMS) as internal standard. Chemical shift, delta δ in ppm was recorded.

### Triton WR 1339 induced anti-hyperlipidemic activity

Seventy two rats were arranged in 12 groups (6 animals each) and were deprived of food but were allowed free access to drinking water. Group I treated with vehicle (distilled water) served as normal group, in all other groups (II to XII) hyperlipidemia was induced by a single intraperitoneal (ip) injection of triton WR 1339 (300 mg/kg body wt) dissolved in normal saline (pH 7.4)<sup>10</sup>. Group II was kept as control, without any further treatment. Group III was treated with atorvastatin 10 mg/kg body wt. Group IV to XII were treated with Dibenz [c,e] Azepine-5,7-Dione derivatives compound I to IX in dose of 150 mg/kg. The compounds and atorvastatin were administered by oral gavage one hour before the triton administration. Animals were sacrificed 24 h after the administration. Blood was collected from tail vein of each animal and the serum was separated and used for the estimation of serum lipid profile.

### Statistical Analysis

Results were expressed as mean values and standard deviations. The data were analyzed by one way ANOVA followed by and Dunnett's test with triton control group using Prism 3.0. P value less than 0.05 were considered significant.

## RESULT

### Synthesis and characterization of Dibenz[c,e]azepine-5,7-Dione derivatives

Nine derivatives of Dibenz[c,e]azepine-5,7-dione or Diphenimide (C-1 to C-9) were synthesized from Diphenic anhydride or Dibenz[c,e]oxepine-5,7-Dione. Diphenic anhydride was synthesized from anthranilic acid. Characterization of the synthesized compounds were carried out on the basis of chemical data and spectral data.

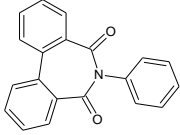
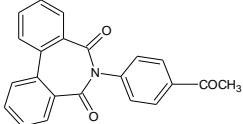
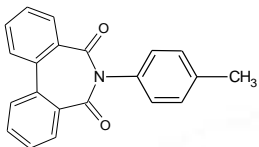
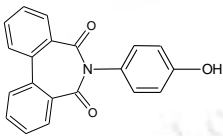
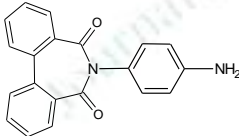
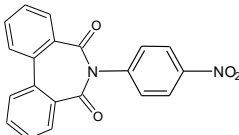
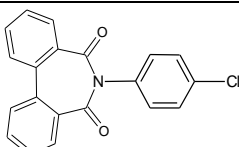
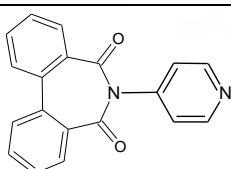
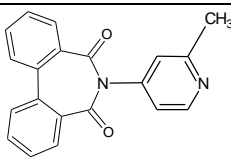
Table 1: Melting point, percentage yield, molecular formula and molecular weight of Dibenz [c, e] azepine-5,7-Dione derivatives.

Compound No.	Molecular formula	Melting point Range (°C)	% Yield	Molecular weight (Da)	Log P value (calculated)
C-1	C <sub>20</sub> H <sub>13</sub> NO <sub>2</sub>	203-05	76.84	299.32	3.79±0.62
C-2	C <sub>22</sub> H <sub>15</sub> NO <sub>3</sub>	242-48	73.82	341.36	3.55±0.63
C-3	C <sub>21</sub> H <sub>15</sub> NO <sub>2</sub>	147-49	68.29	313.35	4.25±0.62
C-4	C <sub>20</sub> H <sub>13</sub> NO <sub>3</sub>	250-52	71.04	315.32	2.96±0.62
C-5	C <sub>20</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub>	192-94	62.35	314.34	2.21±0.63
C-6	C <sub>20</sub> H <sub>12</sub> N <sub>2</sub> O <sub>4</sub>	260-62	74.35	344.32	4.07±0.63
C-7	C <sub>20</sub> H <sub>12</sub> ClNO <sub>2</sub>	219-21	67.71	333.77	4.632±0.63
C-8	C <sub>19</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub>	238-40	65.93	300.31	2.80±0.63
C-9	C <sub>20</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub>	226-28	65.53	314.34	3.26±0.63

Melting point, percentage yield, molecular formula, molecular weight and log p of synthesised compounds are shown in **Table 1**. The Spectroscopic data (IR and

$^1\text{H-NMR}$ ) of synthesised compounds are illustrated in **Table 2**.

**Table 2: Spectroscopic data of Dibenz[c,e]azepine-5,7-Dione derivatives**

Comp.	Structure	Characterisitic IR (KBr) $\text{Cm}^{-1}$	NMR Chemical Shift $\delta$ (ppm)
C-1		1600-1400 Str. (C=C of aryl) 1655 Str. (C=O Imide), 3150-3000 (Str. Ar C=C-H Str.)	6.51 - 7.44 (m, 5H, N-Ar-H) 7.76 -8.21 (m, 8H, Ar-H)
C-2		1690 Str. (Ar C=O )	2.54 (s, 3H, COCH <sub>3</sub> ) 7.78 -7.80 (m, 4H, N-Ar-H)
C-3		2925 Str. (C-H of Ar CH <sub>3</sub> ) 3030 Str.(Ar =C-H)	2.29 (s, 3H, CH <sub>3</sub> ) 7.22 - 7.65 (m, 4H, N-Ar-H)
C-4		3315 Str. (Phenolic OH)	7.04 - 7.38 (m, 4H, N-Ar-H) 9.17 (s, 1 H, Ar- OH)
C-5		3445 Str. (Ar NH <sub>2</sub> ) 3360 Str. (Ar NH <sub>2</sub> ) Due to symmetrical and asymmetrical stretching	5.85 (s, 2H, Ar-NH <sub>2</sub> ) 6.96 - 6.99 (m, 4H, N-Ar-H)
C-6		1360 Str. (N-O of NO <sub>2</sub> ) 1521 Str. (N-O of NO <sub>2</sub> )	7.72-8.49 (m, 4H, N-Ar-H)
C-7		842 Str. C-Cl (Ar-Cl) 1590 Str ( C=C of Ar) 3084 Str. (Ar C-H of C <sub>6</sub> H <sub>4</sub> Cl)	7.37-7.61 (m, 4H, N-Ar-H)
C-8		1670 Str. (C=N of pryidine) 2948-3176 Str. (=CH of Pyridine)	7.75-8.68 (m, 4H, Pyridine-H)
C-9		1662 Str. (C=N of pyridine) 2954-3068 Str. (=CH of Pyridine) 2850-2750 Str, ( CH <sub>3</sub> of Pyridine)	2.70 (s, 3H, CH <sub>3</sub> with pyridine) 7.51-8.42 (m, 4H, Pyridine H)

**Table 3:** Effect of different derivatives of Dibenz[c,e]azepine-5,7-Dione on serum lipid levels in Triton WR-1339 (TRI) induced hyperlipidemic rats.

Groups	Treatment dose (mg/kg)	Total Cholesterol (mg/dl)	Triglyceride (mg/dl)	HDL-C (mg/dl)	LDL-C (mg/dl)
Normal	Vehicle	82.83±4.64	96.08±4.37	36.17±2.95	29.83±2.37
Triton control	300	388.17±6.37	529.08±7.71	24.33±1.43	145.33±5.85
Triton +Atorvastatin	10	151.17±6.48	375.17±5.49	33.42±1.21	45.17±2.52
Triton + C-1	150	294.33±18.96*	479.50±15.44*	29.33±1.41*	110.17±8.04*
Triton + C-2	150	380.67±9.26	524.42±8.60	25.17±1.11	133.17±3.72
Triton + C-3	150	281.17±7.32*	433.04±20.93*	30.67±0.92*	87.33±5.27*
Triton + C-4	150	262.33±7.20*	376.08±10.92*	32.17±1.19*	65.50±1.06*
Triton + C-5	150	274.17±8.42*	426.33±19.45*	31.33±1.05*	69.33±1.99*
Triton + C-6	150	391.50±7.36	517.33±7.41	24.67±1.52	138.83±4.92
Triton + C-7	150	368.83±6.05	519.83±6.61	25.83±1.17	139.67±5.41
Triton + C-8	150	386.17±6.70	516.50±13.37	25.17±1.56	135.33±11.56
Triton + C-9	150	372.33±13.94	501.50±10.92	26.17±1.01	140.33±8.24

Values reported as Mean ± SEM (n=6). The data were analyzed by one way ANOVA followed by and Dunnett test. \*P<0.05 as compared with triton control group.

### Antihyperlipidemic Activity

#### Induction of Hyperlipidemia by Triton WR-1339

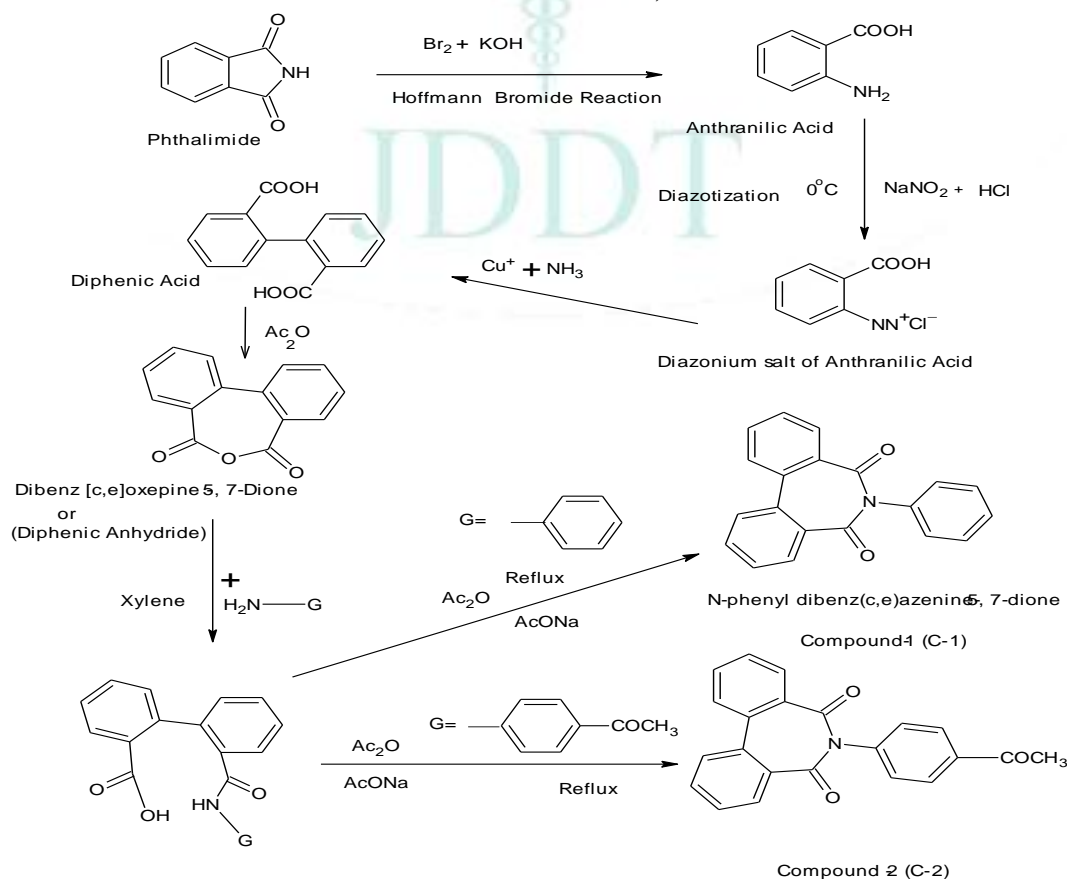
The levels of plasma total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL) and low-density lipoprotein (LDL) levels of all groups treated for 24 h after Triton administration are shown in Table 3. In comparison with the normal group, Triton WR-1339 caused a significant increase in TC, TG and LDL measured 24 h after Triton injection. Triton WR-1339 caused a significant decrease in HDL cholesterol levels in the hyperlipidemic control (HG), at 24 h after Triton administration, in comparison with the normal group (Figure 3-6 and Table 3).

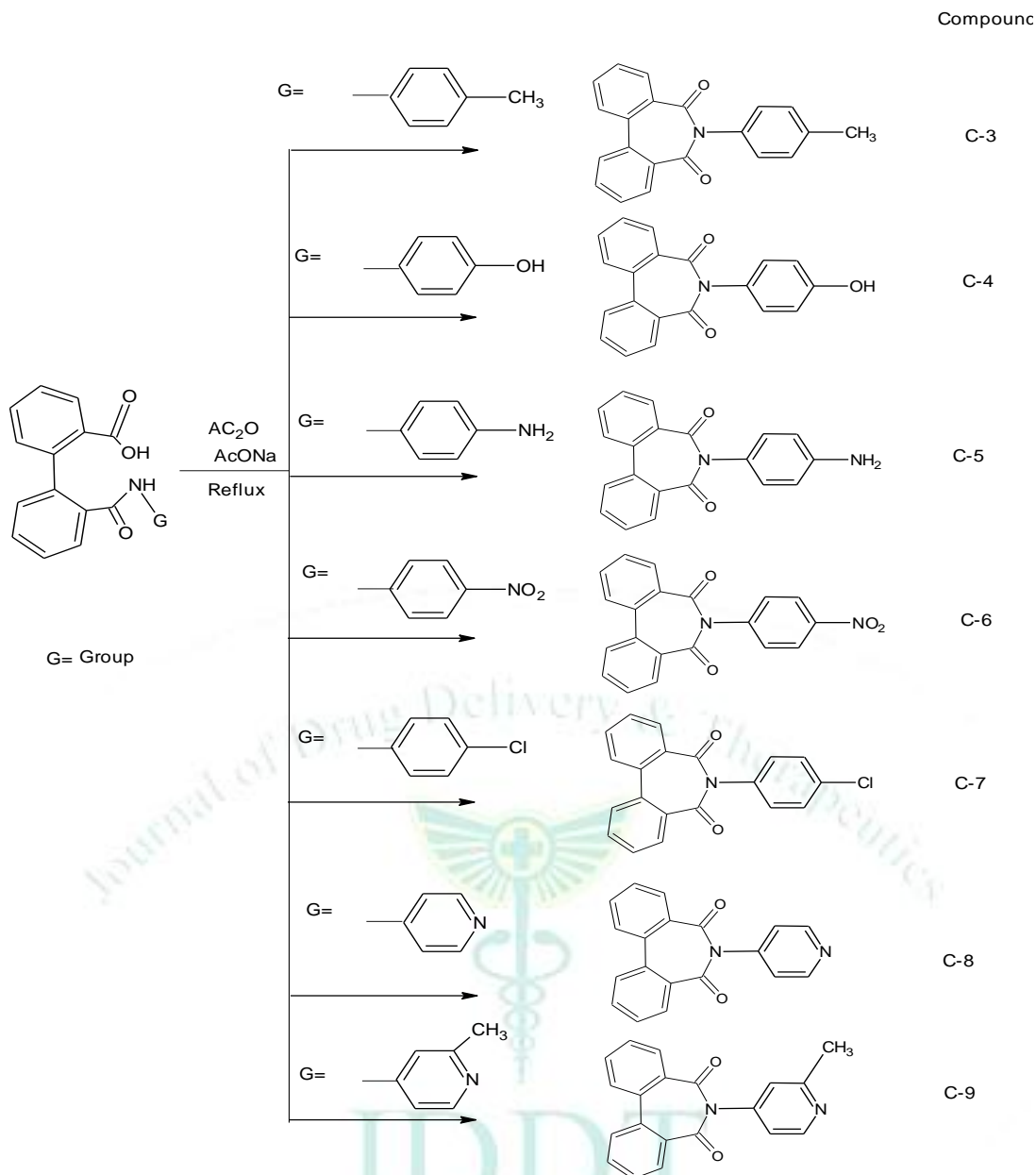
#### Effect of synthesized compounds (C-1 to C-9) on plasma level of Total Cholesterol (TC), Triglyceride (TG) and Low Density Lipoprotein (LDL)

The oral administration of Dibenz[c,e]azepine-5,7-Dione derivatives compound 1,3, 4 and 5 to rats significantly (P<0.05) decreased the plasma level of TC, TG and LDL in comparison to the triton control group (Figure 3,4,5 and Table 3).

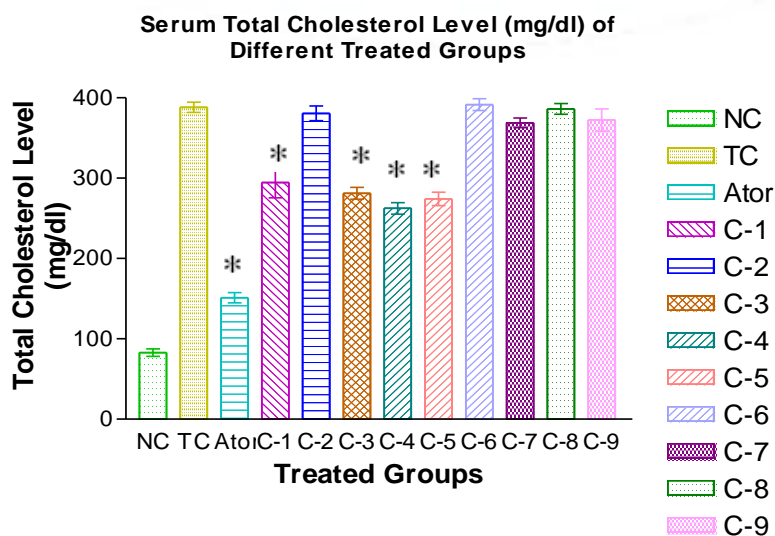
#### Effect on plasma level of HDL

The plasma level of HDL-C significantly increased (P<0.05) in rats treated with compound 1,3, 4 and 5 in comparison to the triton control group (Figure 4 and Table 3).

**Figure 1:** Scheme for synthesis of Dibenz[c,e]azepine-5,7-Dione derivatives compounds one and two

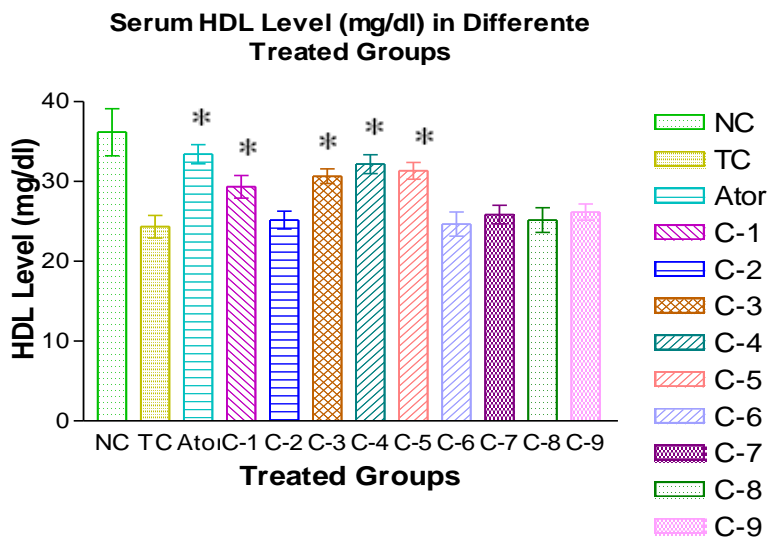


**Figure 2:** Scheme for synthesis of Dibenzo[c,e]azepine-5,7-Dione derivatives compounds three to nine.

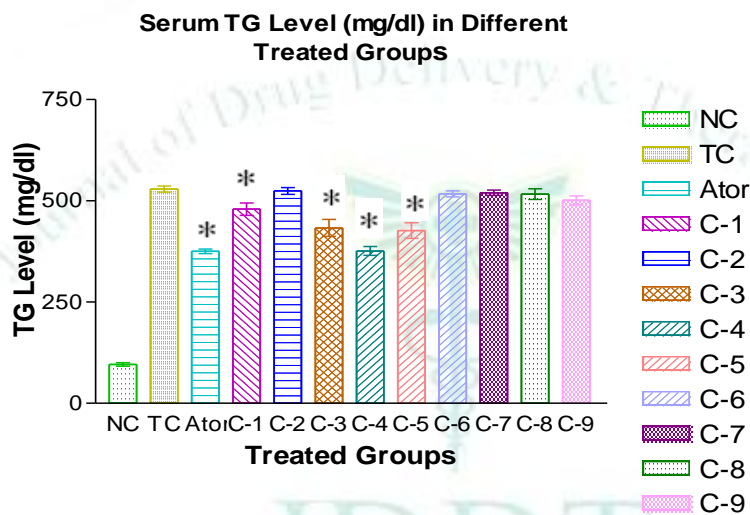


**Figure 3:** Effect of different derivatives of Dibenzo[c,e]azepine-5,7-Dione on total cholesterol in Triton WR-1339 (TRI) induced hyperlipidemic rats. (NC: Normal control, TC: Triton control, Ator: Atorvastatin, C-1,2,3,4,5,6,7,9 : Test compound 1,2,3,4,5,6,7,9), \*P<0.05 as compared with triton control group.

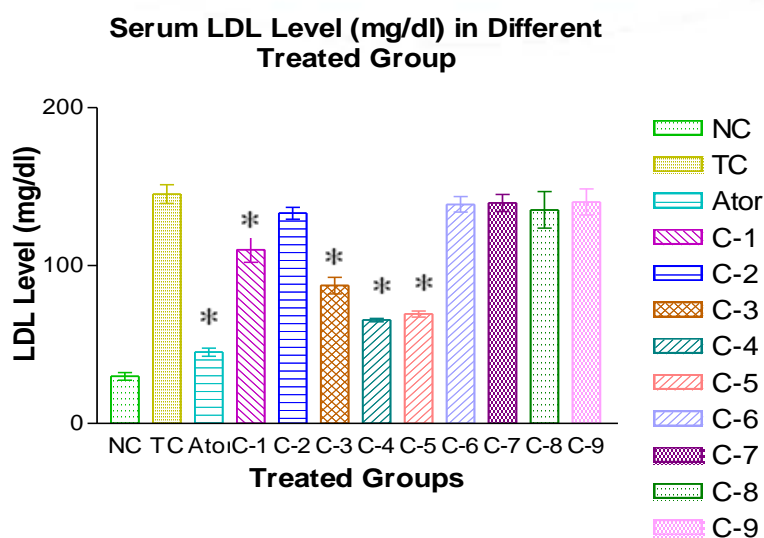




**Figure 4:** Effect of different derivatives of Dibenz[c,e]azepine-5,7-Dione on HDL level in Triton WR-1339 (TRI) induced hyperlipidemic rats. (NC: Normal control, TC: Triton control, Ator: Atorvastatin, C-1,2,3,4,5,6,7,9 : Test compound 1,2,3,4,5,6,7,9), \*P<0.05 as compared with triton control group.



**Figure 5:** Effect of different derivatives of Dibenz[c,e]azepine-5,7-Dione on triglyceride level in Triton WR-1339 (TRI) induced hyperlipidemic rats. (NC: Normal control, TC: Triton control, Ator: Atorvastatin, C-1,2,3,4,5,6,7,9 : Test compound 1,2,3,4,5,6,7,9), \*P<0.05 as compared with triton control group.



**Figure 6:** Effect of different derivatives of Dibenz[c,e]azepine-5,7-Dione on LDL level in Triton WR-1339 (TRI) induced hyperlipidemic rats. (NC: Normal control, TC: Triton control, Ator: Atorvastatin, C-1,2,3,4,5,6,7,9 : Test compound 1,2,3,4,5,6,7,9), \*P<0.05 as compared with triton control group.

## DISCUSSION

Triton WR-1339 acts as a surfactant and suppresses the action of lipases to block the uptake of lipoproteins from circulation by extra hepatic tissues, resulting into increased blood lipid concentration [Kumar]. The biphasic nature of triton-induced hyperlipidemia is helpful in understanding the mode of action of hypolipidemia agents. Drugs interfering with lipid biosynthesis or uptake will be active in the synthesis phase.

In searching for a new class of antihyperlipidemic agents, many compounds having open imide or cyclic imide function have been found to possess antihyperlipidemic action via lowering the triglycerides and cholesterol levels. Some Dibenz[c,e]azepine-5,7-Dione compound are more superior in many cases than clofibrate.

In this study, cholesterol, triglyceride and LDL levels were found to be elevated 24 h after the triton WR-1339

administration which was effectively decreased by treatment with oral administration of Dibenz[c,e]azepine-5,7-Dione compounds 1,3, 4 and 5. The reduction of plasma cholesterol and triglyceride in test compound treated rats was associated with a decrease in LDL (Patel et al., 2003). These findings suggest that the cholesterol-lowering activity of test compound probably mediated through HMG-CoA reductase activity or lipoprotein lipase activity, responsible to decrease plasma triglycerides levels<sup>11</sup>. However, more studies are needed to identify the exact mechanisms of the compound 1, 3, 4 and 5.

## CONCLUSION

In conclusion, it may be stated that the results of the present study demonstrated new properties of synthesized derivatives of dibenz[c,e]azepines-5,7-diones as potent lipid lowering agents and these beneficial activities may contribute to their cardioprotective and antiatherosclerotic role.

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